INSTRUCTOR'S GUIDE
for the "Botulism in Argentina"
Computer-Based Case Study

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I. Ideas for Using "Botulism in Argentina" in the Classroom Setting

"Botulism in Argentina" was developed as a self-instructional training module for students to complete independently on their own time and at their own pace. A student with the prerequisite skills and knowledge should be able to download the files, run the case study, answer at least 70% of the questions correctly, and fulfill each of the learning objectives on their own.

Although designed to be self-instructional, "Botulism in Argentina" also provides several options for use in a classroom setting. Classroom instructors might consider employing the case study in the following ways:

- **Use explanations, descriptions, and examples from the case study to supplement lectures and training exercises.** Instructors can borrow freely from the case study and the related materials in developing their own lectures and training exercises. The case study itself provides many specific examples of how a real-live outbreak unfolds or how to approach an outbreak investigation. The "More About" lessons and "Explore with an Expert" vignettes provide succinct descriptions of basic epidemiologic and public health concepts. In addition, a modified version of the Epi Info database created in the original investigation can be used by students to practice their computer analysis and data interpretation skills.

- **Work through the case study as a class, either in steps corresponding to the instructor's lectures or as one extended exercise.** In this approach, the instructor and/or students can read the case study text aloud to the class, moving from page to page. Students can take turns answering the questions or add to or critique the answers given by others. Students can ask questions about things they don't understand. The instructor can note where the investigation deviates from the routine.

- **Have students do the case study as homework (or a test) to reinforce concepts covered in class.** After the instructor has completed didactic lectures on related epidemiologic and public health concepts (e.g., outbreak investigation, study design, data analysis, epidemic curves), students can independently work through the case study. This will test the student's understanding of the basic concepts and his/her ability to apply them to a real world setting. In a subsequent class, the instructor can answer questions, review concepts that remain puzzling, and lead discussions on the more controversial topics. (See "Topics for Further Discussion with Students".)

  [NOTE: After completing each step of the case study, the student can clear his or her answers and repeat the step to improve his/her score. Only the "best" score is maintained by the computer. As a result, the scoring provided through the case study cannot be used as a true test score.]

II. Resources Offered by "Botulism in Argentina"

- **"More About" Lessons -** these screens review basic epidemiologic and public health concepts necessary for completion of the case study. Topics covered include:
  - Press Releases
  - Epidemic Curves
  - Writing Questions for an Epidemiologic Study
  - Analyzing Results of a Cohort Study
  - Factors Contributing to an Outbreak
  - Measures of Program Effectiveness

- **"Explore with an Expert" Vignettes** - these screens allow students to independently explore interesting epidemiologic, laboratory, or environmental health topics not critical to the case study plot. The topics covered include:
  - Diagnosis of Botulism
  - Laboratory Confirmation of Botulism
  - Which Study to Undertake First
  - Growth of *Clostridium botulinum*
  - Environmental Health Assessments
  - Recommending Control Measures

- **References** - linkages to scientific articles on botulism are included under the References icon. The References icon includes:
  - Shapiro RL, Hatheway C, Swerdlow DL. Botulism in the United States: A Clinical and Epidemiological Review. Ann Intern Med 1998;129:221-228.
  - St. Louis ME, Peck SHS, Bowering D, et al. Botulism from Chopped Garlic: Delayed Recognition of a Major Outbreak. Annals Int Med 1988:108:363-368.
  - Hughes JM, Blumenthal JR, Merson MH, et al. Clinical Features of Types A and B Food-borne Botulism. Ann Intern Med 1981;95:442-445.
  - Centers for Disease Control and Prevention: Botulism in the United States, 1899-1996. Handbook for Epidemiologists, Clinicians, and Laboratory Workers. Atlanta, GA. Centers for Disease Control and Prevention, 1998.
  - Villar RG, Shapiro RL, Busto S, et al. Outbreak of Type A Botulism and Development of a Botulism Surveillance and Antitoxin Release System in Argentina. JAMA 1999; 281:1334-1338,1340.

  The published report of the investigation upon which "Botulism in Argentina" was based (i.e., Villar RG, et al., 1999) is included in the References icon. We suggest, however, that students not read the report until they have completed the case study.

  Excerpts from the Control of Communicable Diseases Manual (Chin, ed., 2000) and "Principles of Epidemiology: An Introduction to Applied Epidemiology and Biostatistics" (a CDC self-study course, 1992) are also included under the References icon. Because these two resources include only parts of the original publications, they will be of limited value. However, students will be well served to become familiar these references and may wish to obtain the complete works.

- **Epi Info Database** - the case study includes a modified version of the database from the original "Botulism in Argentina" investigation. (All patient identifiers and extraneous variables have been deleted.) Students can practice their Epi Info analytic skills (Epi Info 6 or Epi Info 2000) using the database and compare their output to completed analyses provided under the Epi Info icon.

  The file names of the database are C:\CB_3058\epiinfo\botulism.rec (Epi Info 6) and C:\CB_3058\epiinfo\botulism2000.mdb (Epi Info 2000). Students will need to install Epi Info on their computers before beginning the analysis. The latest versions of Epi Info can be obtained free of charge at www.cdc.gov/epiinfo.

III. Additional Background on Selected Epidemiologic Concepts

The case study is rich in specific examples of how one might go about doing some aspect of an outbreak investigation or an epidemiologic study. Instructors should not feel that the case study illustrates the only way (or even the best way) a problem could have been approached. Nor should an instructor assume that the case study highlights all of the important issues in an investigation. Instructors should be prepared to discuss the broader context of some key concepts. The following background information may be useful:

- **Steps of an Outbreak Investigation**
  A variety of "Steps of an Outbreak Investigation" exist in the epidemiologic training literature. In this case study, we combine activities into six basic steps. In "Principles of Epidemiology: An Introduction to Applied Epidemiology and Biostatistics", the author uses a detailed 10-step approach to prevent public health practitioners from omitting any important activity. Other authors use other series of steps.

"Botulism in Argentina"	"Principles of Epidemiology"
- Detect an outbreak - Generate hypothesis - Design epidemiologic study to test hypothesis - Analyze and interpret data - Execute other studies - Implement control and prevention measures	- Prepare for field work - Establish the existence of an outbreak - Verify the diagnosis - Define and identify cases - Perform descriptive epidemiology - Develop a hypothesis - Evaluate the hypothesis - Reconsider/refine hypothesis and execute additional studies - Implement control and prevention measures - Communicate findings

  There is no universally agreed upon approach to an investigation. Furthermore, in real-life, the order of activities in an investigation will vary with the outbreak and surrounding circumstances. Steps can overlap and merge together. Some steps may be skipped entirely; other steps may be repeated numerous times.

What students must understand is that in undertaking an outbreak investigation, one must work systematically through the issues. Steps can be omitted or rearranged, but they should not be overlooked due to the urgency of the moment.

- **Detection of an Outbreak**

  In "Botulism in Argentina", the Ministry of Health became aware of the botulism outbreak due to notification by a local health care provider. Astute health care providers who recognize and report an unusual disease or disease pattern are critical to public health surveillance. Their reports can alert the health department to a problem long before it would become aware of the problem through other channels. This early detection allows the health department to begin an investigation and implement control measures more quickly, thereby preventing additional morbidity and mortality.

  Reports from a health care provider are not the only means by which outbreaks are detected. Outbreaks can come to the attention of the health department through:
  - increase in reports of a disease through routine surveillance (or changes in patterns of disease occurrence)
  - increase in requests for particular laboratory tests or the isolation/detection of particular pathogens
  - calls from health care providers (as in "Botulism in Argentina")
  - increased requests for treatments (e.g., botulinum antitoxin) or use of particular over-the-counter pharmaceuticals
  - calls from private citizens who have been affected by an illness or know of friends or family who have been affected

  The usefulness of these means of outbreak detection relies heavily on the accuracy and timeliness of the information. Errant reports can lead the health department to waste precious resources investigating a "non-problem" and divert their attention from more important matters.

  In the detection of a possible outbreak, public health practitioners need to consider the reports and source(s) of information carefully. Before launching a full investigation, an investigator will typically review the reported cases to determine if they are likely to represent a single disease and take steps to confirm the diagnosis. If this information is supportive of an outbreak, additional investigative steps may be undertaken.

- **Defining a Case (Laboratory vs. Clinical Findings)**

  A case definition is a standard set of criteria for deciding whether an individual should be classified as having the disease of interest in an epidemiologic investigation. A case definition includes clinical criteria (e.g., signs, symptoms, and laboratory tests) and restrictions on time, place, and person. The hypothesis being tested (e.g., eating at the home at the terminal stop of the bus route) should NOT be included in the case definition.

  Laboratory criteria increase the specificity of a case definition (i.e., reduce the number of persons not having the disease but meeting the case definition). This reduces misclassification and maximizes the ability of a study to detect the source of an outbreak.

  However, laboratory confirmation will exclude patients who did not see a physician or were not tested, thereby, decreasing the sensitivity of the case definition and number of cases included in the study.

Furthermore, laboratory confirmation may not be available early in an outbreak. As a result, investigators may use a clinical case definition initially in an investigation and refine the definition when laboratory information becomes available.

For the retrospective cohort study undertaken in "Botulism in Argentina," investigators defined a case of botulism as:

- a bus driver from the morning shift of the implicated bus route (PERSON/PLACE CRITERIA)
- with cranial nerve dysfunction (e.g., blurred vision, drooping eyelids) (CLINICAL CRITERIA)
- with onset of symptoms between January 5 and 15 (TIME CRITERIA)

Given that acute neurologic problems are unlikely to occur among bus drivers (i.e., healthy young- to middle-aged men) and that a few of the cases were confirmed by laboratory testing, use of clinical features of the disease (without laboratory confirmation) for the case definition is logical. Moreover, use of laboratory criteria in the case definition might have actually hindered the search for the source of this outbreak. If investigators had limited cases to the three patients with laboratory confirmation, the power of the study would have decreased dramatically. Conversely, if investigators had made an effort to confirm each of the cases with laboratory testing, it could have been expensive and might have delayed the results of the epidemiologic study.

- **Means to Identify Additional Cases**

  The success of an outbreak investigation depends largely on identification and inclusion of as many cases as possible in the analysis of information. Cases identified early in an investigation (i.e., those initially brought to the attention of public health workers) may be unusual in some way. They may only be the "tip of the iceberg", misrepresenting the size and distribution of the outbreak, or their characteristics may be unique (e.g., only hospitalized patients, patients at risk for poor outcomes of the disease, secondary cases). Public health workers must "cast the net wide" and identify as many cases as possible to accurately characterize an outbreak (e.g., the geographic extent of the problem and the population affected by it) and its cause(s).

  In "Botulism in Argentina", the Ministry of Health used three ways to detect additional cases (including the press release). Here is a more complete list of case detection methods:

  - talk with the cases to identify other people who may have shared food/meals with them (or who have similar symptoms)
  - talk with family members and friends who may have shared meals with the cases and ask if any have signs/symptoms of botulism
  - talk with co-workers who may have shared meals with the cases and ask if any have signs/symptoms of botulism
  - contact local hospitals and emergency rooms, describe signs/symptoms suggestive of botulism, and ask that all similar cases of acute neurologic illness be reported to the Ministry of Health
  - review admission and emergency room logs at local hospitals for patients with admitting diagnoses suggestive of an acute neurologic disease (e.g., stroke, myasthenia gravis, Guillain-Barré syndrome) and follow-up suspicious patients to determine if botulism is a possibility
  - contact local physicians (especially neurologists), describe the signs/symptoms suggestive of botulism, and ask that all similar cases of acute neurologic illness be reported
  - contact area laboratories that do testing for botulism and ask to be notified of all requests for botulism testing (NOTE: few laboratories do testing for botulism so this may be an unlikely source for identifying cases)
  - notify the public of the outbreak through various forms of media (e.g., newspapers, radio, television)

Investigators need to be creative, aggressive, and diligent in identifying sources of possible cases. In pursuing the sources, however, they should also balance the time (and other costs) with the likely productivity of using a particular source.

- **Analyzing Data**
  "Botulism in Argentina" greatly simplifies ("oversimplifies") the analysis of data during an outbreak investigation. The analyses (Step 4) go almost directly from someone else inputting the data in Epi Info to a fill-in-the-blank question about the cause of the outbreak. Although tempting, an investigator should not jump to the obvious data analyses (that is those they think will show the source of the outbreak). Nor should an investigator "do a data dump" (e.g., blindly producing all possible frequencies and cross-tabulations of the data). Rather, the investigator should systematically analyze the data in a logical, predetermined fashion.

  The following approach to data analysis is adapted from the cogent analytic strategy described by Richard Dicker, MD, MPH in Field Epidemiology (1996):
  1) Establish how the data were collected and plan to analyze accordingly.
  2) Review data for missing and nonsensical values (e.g., values out of the expected range or not fitting with other information in the record) and make edits.
  3) Identify the most important variables in light of what you know about the subject matter, biologically plausible hypotheses, and manner in which the study was conducted.
  4) To characterize the study population and case-patients, create tables of clinical features and descriptive epidemiology.
  5) To assess exposure-disease associations, create two-way tables based on study design, prior knowledge, and hypotheses.
  6) Create three-way tables, refinements (e.g., dose-response), and subgroup analyses based on design, prior knowledge, hypothesis, or interesting findings in the data.

- **Using Epi Info**
  A modified version of the database from the original "Botulism in Argentina" investigation is included in the case study. Students can analyze the data using Epi Info 6 (datafile name: C:\CB_3058\epiinfo\botulism.rec) or Epi Info 2000 (datafile name: C:\CB_3058\epiinfo\botulism2000.mdb).

  In the database, the variable CASE indicates whether a person was a case or not. It has the values "CASE" and "NOT A CASE". The remaining variables (excluding age and gender) are coded as "1"= YES and "2" = NO.

  Students will need only a few basic commands to analyze the data such as SELECT, LIST, FREQ, MEANS, TABLES, DEFINE, and IF/THEN. Student analyses should include:
  - a line list of selected variables for cases
  - a frequency of gender among cases
  - age distribution and median age among cases
  - an epidemic curve
  - a frequency of botulism symptoms among cases
  - a comparison of attack rates between those who did and did not eat various foods served at the terminal home of the bus route

  Because food consumption at the terminal home of the bus route was collected for each day of the

period of interest, students will need to define a new variable that indicates if the individual ate a particular food on any of the days.

Students can check their analyses (or their interpretation of the analyses) by comparing them with analyses provided under the case study Epi Info icon.

- **Interpretation of Data**
  "Botulism in Argentina" treats the interpretation of the investigation results rather superficially. The key findings were:
  - A statistically significant elevated relative risk was found only for matambre.
  - All of the cases ate the matambre.
  - Environmental health studies revealed a host of problems in the production of this food item.

  No time, however, was taken to critically question the findings and how they fit together. Furthermore, chance, selection bias, information bias, confounding, and investigator error should all be evaluated as possible explanations for an observed association.

  Even with a "perfect" epidemiologic study, however, it is the weight of evidence (not a single number) that ultimately must be used in determining the source of an outbreak. The following criteria are commonly cited in drawing conclusions from scientific studies and taking action: (R. Dicker, 1996)
  - strength of the association
  - biological plausibility
  - consistency with other studies/evidence
  - exposure preceded disease
  - dose-response effect

  In a foodborne disease outbreak, assessing the weight of evidence from the investigation is crucial. It requires an understanding of the causative agent and its behavior in food and a detailed reconstruction of the events surrounding the food processing and preparation. It also requires critical thinking and acknowledgment of investigation limitations. Investigators must ask themselves: "Is there solid epidemiologic evidence linking the outbreak and the implicated product?" "Does the outbreak match the distribution of the implicated food?" "Is the outbreak explained by problems found in the food preparation?" "Does basic food research support the likelihood of the organism growing/surviving/producing toxin in the implicated food?" Only after analyzing available information in this critical manner can investigators expect to make sound judgements about the source of an outbreak.

IV. Topics for Further Discussion with Students

The format of the case study required questions to be written such that the answers could be judged as correct or incorrect by the computer. Some questions included in the case study, however, were difficult to present in a multiple-choice format. Furthermore, the case study did not capture the urgency to find an answer, a feeling common in this sort of investigation particularly when faced with a deadly disease such as botulism. As a result, the student was not always challenged with the reality of the situation or the complexity of the investigation.

Students should be encouraged to revisit and think more seriously about selected parts of the case study.

They should work systematically through the issues, consider the pros and cons of each answer (including the ramifications of any action), and be ready to defend their answers.

Questions that fit into this category:
Step 1: (Question 5) At this point, would you suspend commercial food services conducted at the home at the terminal stop of the bus route? (Have students vote "for" or "against" action. Then create a list of pros and cons for taking action.)

Step 2: (Question 10) What type of study would you use to investigate this hypothesis? (Students should be asked what other studies they would consider at this point and why. They should not limit themselves to the four studies listed as possible answers. They should also keep in mind the time and resource limitations present in most health departments.)

Step 3: (Question 14A) How would you ask a bus driver if he had eaten salami at the home at the terminal stop of the bus route. (Discuss the finer points of question development including specific wording and enumeration of possible responses.)

Step 4: (Question 17) Interpret the results of the cohort study. Which food served at the terminal home of the bus route was associated with illness? (Students should be challenged to give reasons why the matambre might not be the source of the outbreak. They should methodically discount chance, selection bias, information bias, confounding, and investigator error.)

Step 5: (Question 19) As part of the environmental health assessment, which of the following activities might you undertake? (Students should try to imagine what it would be like to do an environmental health assessment and how they would accomplish some of the suggested activities [in very practical terms].)

Step 6: (Question 22) In addition to shutting down the matambre producer, what other control measures would you recommend at this time? (Students should be encouraged to consider the feasibility of undertaking each measure [including barriers]; the acceptability to persons affected, the community, and decision makers; the impact; and the cost-effectiveness.)

Step 6: (supplement to Question 22) What is the true scope of this problem? (Students should think carefully and answer the following questions: Is the problem likely to be limited to the implicated producer, the market that sold the matambre, and the home that served it? Or is something systemically awry affecting the wider food service community? If so, should new regulations be considered that require food processors to get specific training or inspections before they go into business? If not, how many more similar events would it take before the public demands stronger food safety regulations?)

Step 6: (Question 26) Do you think the increase in botulism cases in 1998 indicates that the Botulism Surveillance and Antitoxin Release Program had failed? (Although the answer is "No", students should be asked to consider reasons why the program may be ineffective.)